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COMPARISONS OF MONOSINUSOIDAL WITH BISINUSOIDAL (TWO-WAVE) ANALYSIS *

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*Report No. 79-29, supported in part by the Naval Medical Research and Development Command, under research work unit MR041.01.03-0152. The views presented in this paper are those of the authors. No endorsement by the Department of the Navy has been given or should be inferred.

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† Dr. Lubin died on 9 October 1976. He was on the staff of the Naval Health Research Center. He is included as an author because of his important contribution to this study.

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Body temperature rises slowly from a morning low to an early evening peak; starts to decline rapidly well before habitual bedtime, and continues to decline to a minimal value the next morning[3,4,9] (see Figure 1). Time interval between a trough and a peak of the body temperature curve is

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Figure 1 About Here

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much longer than that between the peak and the next trough.

When a single cosine wave of 24 hour/cycle is fitted to body temperature data[7,8,15], estimates of time-of-peak (TOP) and of time-of-trough (TOT) are usually poor and they are separated by many hours from peak and trough of raw data.

Few methods can be used to improve estimation of TOP and TOT. One such improvement is based on the mathematical theory that any arbitrary repeating waveform can be reproduced completely as a sum of harmonic components found in that waveform. Rummel and his colleagues[12] started their analysis by detailed harmonic analysis of data. Then, a computer program searched for the "best" combination of the harmonics, which described the largest variance in the data with the fewest possible number of harmonics. Although Rummel and his associates' method yielded an interesting combination of two or more harmonic components to describe the data, its feature of automatic selection sometimes resulted in too many frequencies. Instead of automatic selection, Tong and others[15] preselected two waves, 24 hours/cycle and 12 hours/cycle cosine waves, to describe the circadian cycle in survival time after experimental chemotherapy of cancer in mice. They have reported that bisinusoidal or two-wave analysis produced a more precise estimation of TOP (or orthophase angle) and TOT (or bathyphase angle). Recently Colquhoun and others[5] applied this two-wave method to analyze body temperature data obtained from two groups of subjects with satisfactory results. As a natural extension of two-wave method, Lubin used trisinusoidal fit to describe oral temperature. He chose 8 hours/cycle component as the third wave, with a minimal improvement in fit (Lubin, personal communication).

Another method of promise in improving estimates of TOP and TOT is reported by Batschelet who suggested that a "skewed" sinusoidal wave should be fitted to nonsinusoidal waveform, but his method is not yet extensively applied to data.

Purpose of this paper is to compare two-wave method of combining 24 hours/cycle and 12 hours/cycle waves with monosinusoidal method, and to show advantages as well as limitations of the two-wave method. Two sets of body temperature data were used to illustrate the differences between these two methods.

MATERIALS AND METHODS

The first set of data was obtained by Kanabrocki and others[9] and later published[13]. In this data set, body temperature of 13 young soldiers (ages 22 to 28, average of 25.1) were measured at three hourly intervals throughout one 24 hour period, starting from 1900 and continuing to 1600 of the next day, a total of 8 data points per subject. During this period the soldiers did not engage in strenuous or unusual activity and ate meals at 0830, 1430 and 1630. The second data set was from a group of 73 young Royal Navy ratings who followed a normal civilian non-shift working routine; rise at 0630 - 0700, lunch 1200 - 1300, evening meal 1700 - 1800, and lights out at 2300. Body temperature was observed hourly from 0800 to 2300, and then at 0100, 0300, 0500 and 0700. In this study the first data set is called Kanabrocki-Scheving's and the second Blake-Colquhoun's.

For the purpose of fitting cosine wave of 24 hour/cycle and cosine wave of 12 hour/cycle singularly one at a time, and then combined, a computer program was written in FORTRAN IV. The details of the FORTRAN program is available elsewhere[8,10]. A PDP-12 computer with floating point processor was used for the analysis of Kanabrock-Scheving data. For the analysis of Blake-Colquhoun data, an IBM 360 was used for ease of data handling. The analysis was performed on each individual subject.

Goodness-of-fit of the model to the data was measured 1) by a percentage of total variance described by each curve (R^2 or percent rhythm, PR), and 2) by statistically evaluating temporal sequence of the residuals with Run test[6]. In testing a null hypothesis that an observed time sequence of residuals is random, an approximation method to normal distribution was used.

For one-wave analysis, acrophase angles and amplitudes of all subjects were summarized by plotting a 95% confidence ellipse together with calculation of 95% confidence intervals for group acrophase angles and amplitudes[1,7,14]. For two-wave analysis, theoretical values of the best-fitting combined curve were determined for each and every minute of a 24 hour period, then the maximal and minimal values were searched to find TOP and TOT. Amplitude for the TOP was calculated by subtracting the mesor from the maximal value, while amplitude for TOT was calculated by subtracting the theoretically minimal value from the mesor. A 95% confidence ellipse for TOP was produced, along with computation of 95% confidence intervals for amplitudes and orthophase angles. Similarly, a 95% confidence ellipse was produced for TOT. A program set to drive an incremental digital plotter for drawing a 95% confidence ellipse was written in FORTRAN IV for a PDP-12[11].

To determine if the TOP estimated with two-wave fit was significantly different from the TOP obtained with one-wave method, each subject was represented by the polar coordinate values of sine and cosine. These values obtained from two-wave fit were subtracted from the coordinate values estimated with one-wave fit. Resulting differences were, then, subjected to another cosinor analysis to produce a plot of a 95% confidence ellipse. If two-wave analysis differed consistently from one-wave analysis by delaying (or advancing) time-of-peak, the 95% confidence ellipse of these differences was expected not to include the zero[1,14].

RESULTS

Analysis of Averages Across Subjects.

Figure 1 shows statistical analysis of the average body temperature of Kanabrocki-Scheving data (left graph) and of Blake-Colquhoun (right graph). Raw data of both sets show nonsinusoidal waveform, as mentioned previously.

The best fitting one-wave curve to Kanabrocki-Scheving data was: $Y_i = 97.687 + (0.993)(\mathrm{Cos}((360/24)t_i - 240.270)) + e_i$, with TOP of 1601 and TOT of 0401. Percent rhythm was 91.28. The best fitting two-wave curve was: $Y_i = 97.695 + (1.007)(\mathrm{Cos}((360/24)t_i - 239.75) + (0.207)(\mathrm{Cos}((360/12)t_i - 124.25)) + e_i$ with its TOP at 1734, and TOT at 0314. Percent rhythm was 95.75. An improvement in percent rhythm between one-wave and two-waves fit was 4.5% This was very small considering the added cost of the two-wave method which employed two more "predictors" in the sense of multiple regression[2,10]. In sharp contrast to the small gain in the percent rhythm, the difference between these two methods became more marked in terms of precision in estimating time of daily minimum and maximum: a difference of as much as 1 hour 33 min for TOP and smaller but still a clear difference of 47 min in TOT.

Similar analysis was performed on Blake-Colquhoun data, after body temperature data were averaged over 73 subjects. The best fitting curve of 24 hour/cycle was: $Y_i = 97.82 + (0.539)(\text{Cos}((360/24)t_i - 258.382)) + e_i$, with TOP at 1711 and TOT at 0511. Percent rhythm was 84.12%. The best fitting two-wave curve was found to be: $Y_i = 97.80 + (0.584)(\text{Cos}((360/24)t_i - 256.75) + (0.217)(\text{Cos}((360/12)t_i - 145.00)) + e_i$, with TOP at 1944, TOT at 0415, with percent rhythm of 98.64. Difference in percent rhythm between one- and two-waves was 14.52%. Difference in TOP was as large as 2 hours 33 minutes. A smaller difference of 56 minutes was observed between one- and two-wave methods for TOT. Two-wave method caused TOP and TOT to be delayed, bringing them closer to the peak and trough in the raw data.

Analysis of Individual Data and Group Summary.

Analysis of individual subjects and a group summary of the results is shown in Figure 2 and Table 1. For Kanabrocki-Scheving data, 95%

Figure 2 & Table 1 About Here

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confidence intervals of TOP and TOT were larger with two-wave method than with one-wave fit. For instance, 95% confidence interval for TOP was greatly lengthened from 1 hour 21 minutes with one-wave method to 3 hours 23 minutes with the two-wave method. Similar comparison of the confidence intervals using Blake-Colquhoun data revealed, however, a much smaller increase: from 45 minutes of the confidence arch for TOP with one-wave method to 64 minutes with the two-wave method. A tendency for the two-wave method to give a wider 95% confidence interval was observed for TOT but to a much less extent. It was observed also that this tendency was greater for Kanabrocki-Scheving data.

Analysis of time sequence of the residuals with Run test indicated a clear superiority of the two-wave method in producing residuals closer to a random sequence than possible with the one-wave method. When the Run test was applied to the residuals of the one-wave fit to Blake-Colquhoun data, it was found that the one-wave fit failed to extract all rhythmic components in 13 out of 73 subjects. In contrast, the two-wave method succeeded in leaving the residuals whose temporal sequences were random for all 73 subjects, satisfying the analysis model where the residual, e_i, must be random.

DISCUSSION

The one-wave model used in chronobiology is expressed by: $Y_i = M + A \text{ Cos } ((360/T)t_i - \phi) + e_i$, where Y_i is an individual's value at time i, M is mesor; A is amplitude (from the peak to the mesor or the mesor to the trough); T is a period of wave in hour; ϕ is acrophase angle when the value of Y_i is maximal; and e_i is random element normally distributed with zero mean.

Rummel and others' method is based on a model of multiple frequencies: $Y_i = M + \sum_{k=1}^{s} A_k \text{ Cos}((360/T_k)t_i - \phi_k) + e_i$, where there are "s" number of frequency components with A_k amplitude, T_k period, and ϕ_k acrophase angles. A relation between chosen periods may or may not be orthogonal to each other. A potential problem with this method is to set up criteria to decide which frequencies and how many frequencies are to be selected. In the present study, a computer algorithm provided by Rummel and others[12] was applied to averages of Blake-Colquhoun data. Their analysis selected automatically 25 hour/cycle and 12 hour/cycle components as the best two-wave selection. This automatic choice was based on a very small difference in a level of significance used as the criterion. A reanalysis showed that combined curve of 25 hour/cycle and 12 hour/cycle was able to account for less than one percent more variance than a combined curve of 24 hour/cycle and 12 hour/cycle.

As a compromise between one-wave analysis and multisinusoidal analysis, a restricted two-wave model is proposed in this study. Out of many possible combinations of two frequencies, a wave of 24 hour/cycle and another wave of 12 hour/cycle were chosen on a priori basis. The restricted two-wave model is: $Y_i = M + A_1 \text{ Cos } ((360/24)t_i - \phi_1) + A_2 \text{ Cos } ((360/12)t_i - \phi_2) + e_i$.

Recently Batschelet proposed a new model which would be useful for defining nonsinusoidal waveform:

$Y_i = M + A \text{ Cos}(\psi + \nu \text{ Cos } \psi) + e_i$, where $\psi = (360/T)t_i - \phi$, and ν is a new parameter to determine a skewness of sinusoidal wave. A preliminary result of application of this model to Blake-Colquhoun data by Batschelet suggested an improved precision in estimating TOP and TOT in comparison with the one-wave method.

When individuals are infrequently observed and only a few subjects are available for a study, as in the Kanabrocki-Scheving data, caution is required in interpreting the results obtained with the two-wave method. Use of the two-wave method doubles the number of predictors, increasing the chance of "overfitting" to the data, where all fluctuations in data are equally weighted and regarded as true signals. Evidence that "overfitting" has occurred is a much larger confidence ellipse obtained with the two-wave method. An interpretative caution is needed also in handling of a 12 hour/cycle component. Little evidence exists currently to impel an acceptance of the idea that a 12 hour/cycle is present in oral temperature independent of 24 hour/cycle activity. On the other hand, little evidence exists to accept that a 12 hour/cycle is a "pseudo frequency" that exists only as a mathematical artifact to encode the nonsinusoidal waveform.

A distinct advantage of using the two-wave analysis is found in its accuracy in estimating TOP and TOT. Also the residual analysis suggests that the two-wave analysis is quite successful in extracting all major oscillatory components in the data.

After weighing advantages and limitations of the one- and two-wave methods, a few conclusions can be drawn tentatively. Given a data set of many observations per subject over many subjects, the two-wave analysis will be the method of choice in circadian cycle studies. Given, however, a small data set, such as Kanabrocki-Scheving case, a cautious application of the two-wave analysis will be recommended if researchers' primary interest is focused on finding TOP and TOT. If researchers are more interested in establishing overall rhythmicity, i.e., period length and strength of periodicity, the one-wave method is much preferred, as it will provide interpretative simplicity and conservative estimates of percent rhythm.

SUMMARY

Monosinusoidal (one) and bisinusoidal (two) waves were fitted to two sets of data: 1) Kanabrocki-Scheving data consisting of 8 data points over a two day period from 13 young soldiers and 2) Blake-Colquhoun data consisting of 20 data points obtained over a 24 hour period from 73 Royal Navy ratings. Results indicated that the two-wave analysis was preferred to a more widely used one-wave method, as it provided more accurate representation of time-of-peak (TOP) and time-of-trough (TOT) in the data.

Temporal sequence of the residuals after the two-wave analysis was found random, revealing its superiority to the one-wave method. Two-wave analysis was observed to have a potential problem in that it could produce "over-fitting" where every fluctuation in data, however extraneous, have equal weight in the analysis. This potential problem was illustrated by a much larger confidence ellipse resulted from the two-wave analysis applied to small scale data. This increased uncertainty in defining TOP and TOT of a group was not seen when a larger data set was used. Two-wave analysis is thus recommended when data basis is sufficiently large, or when a precision determination of individual TOP and TOT is required. When the data basis is limited, use of one-wave analysis is suggested as the method of choice.

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Table 1 Summary of Group Circadian Cycle Analysis

Kanabrocki-Scheving Data

	Analysis	Mean (95% CI)	Mean (95% CI)	% Rhythm ± SD
Peak	One Wave	1558(1522 to 1643)	.989(.725 to 1.259)	79.7 ± 16.6
	Two Waves	1700(1501 to 1824)	.910(.586 to 1.268)	90.6 ± 8.0
Trough	One Wave	0358(0322 to 0443)	.989(.725 to 1.259)	
	Two Waves	0317(0226 to 0408)	1.210(.858 to 1.562)	

Blake-Colquhoun Data

	Analysis	Mean (95% CI)	Mean (95% CI)	% Rhythm SD
Peak	One Wave	1714(1651 to 1736)	.539(.494 to .584)	63.8 ± 14.2
	Two Waves	1922(1847 to 1951)	.549(.486 to .584)	78.0 ± 9.7
Trough	One Wave	0514(0451 to 0536)	.539(.494 to .584)	
	Two Waves	0416(0359 to 0430)	.793(.730 to .856)	

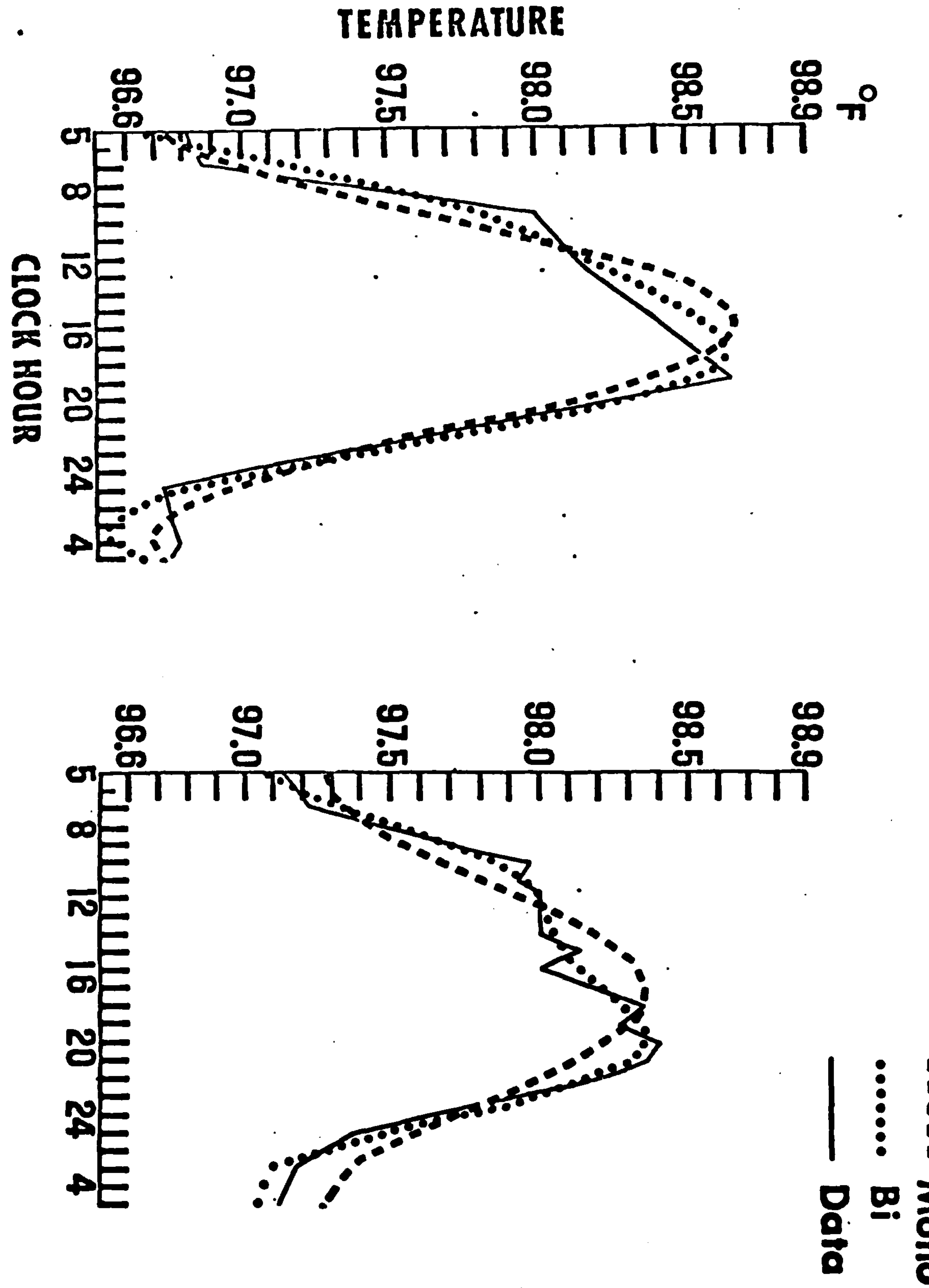

Fig. 1. Average body temperature of the Kanabrocki-Scheving (left) and that of the Blake-Colquhoun (right). Mono = Monosinusoidal or one-wave fit. Bi = Bi-sinusoidal or two-wave fit.

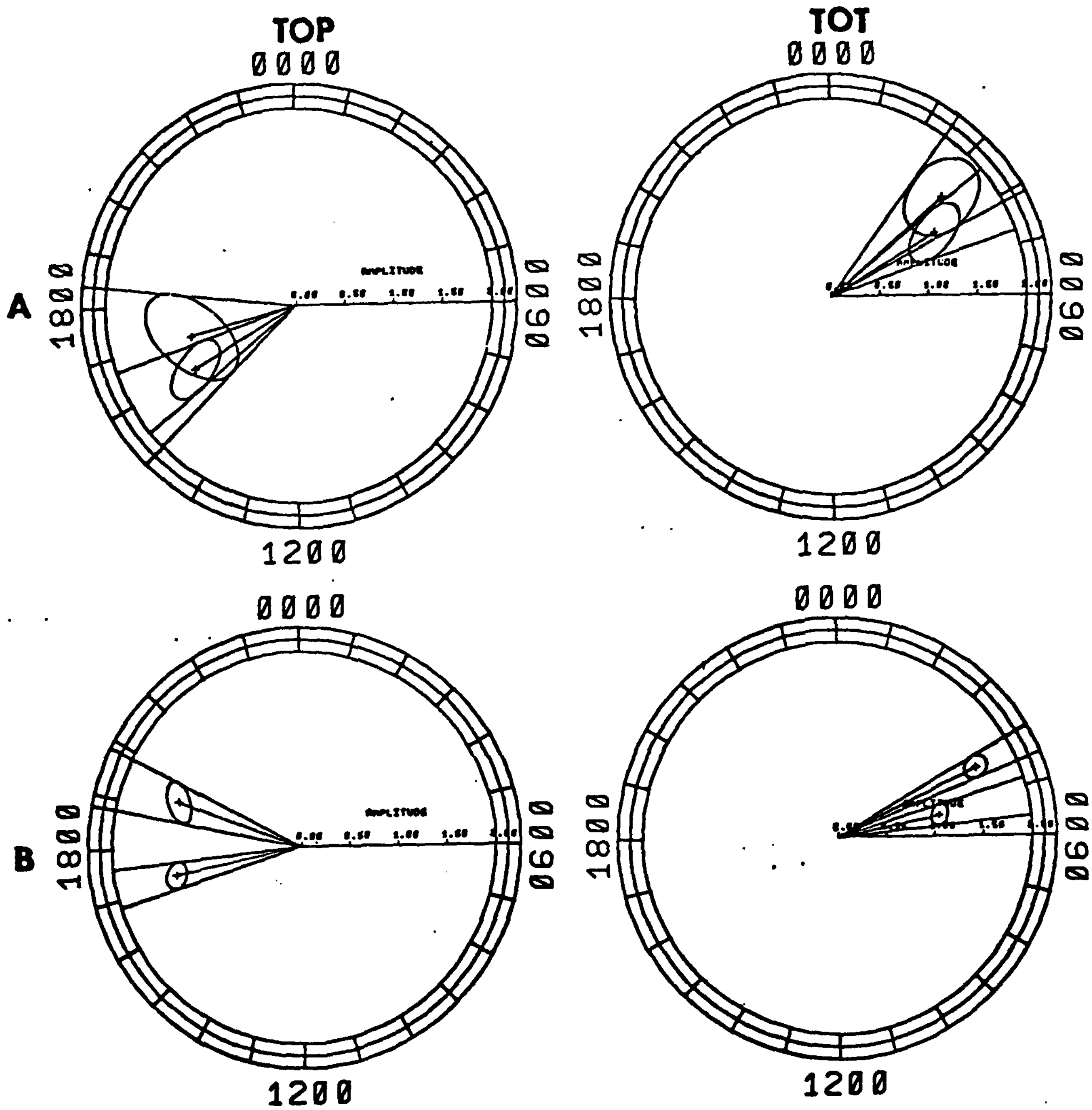

Fig. 2. Cosinor representation of the Kronoback-Scheving data (Top row A, Time-of-Peak cosinor at left, Time-of-Trough at right), and of the Blake-Colquhoun data (TOP shown at the left bottom row B; and TOT shown at the right bottom row B). A 95% confidence ellipse bounded by confidence radii intersecting the outer circle of the clock face are those estimated by two-wave method, while confidence ellipses with shorter radii in defining confidence arcs for TOP and TOT are for estimates obtained with monosinusoidal fit.

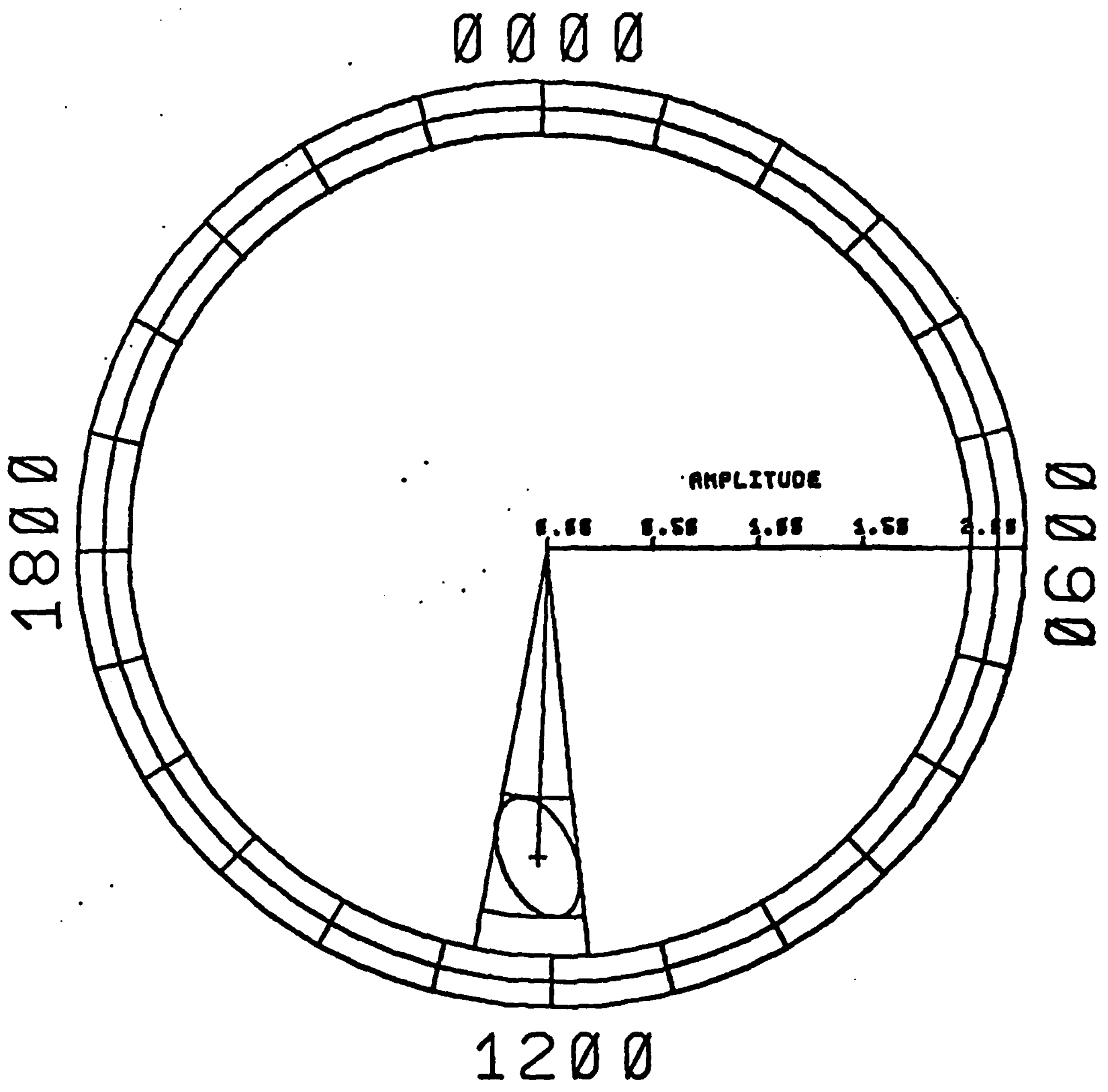

Fig. 3. Statistical analysis of difference between one-wave and two-wave analysis. This cosinor represents differences between two ellipses shown in Cosinor representation of row B left in Fig. 2, showing differences in TOP estimated by one- or two-wave method (the Blake-Colquhoun data).

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER 79-29	2. GOVT ACCESSION NO. A118276	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Comparisons of Monosinusoidal with Bisinusoidal (Two-Wave) Analysis		5. TYPE OF REPORT & PERIOD COVERED Interim
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) P. Naitoh, A. Lubin, W.P. Colquhoun		8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS Naval Health Research Center P. O. Box 85122 San Diego, CA 92138		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS MR041.01.03-0152
11. CONTROLLING OFFICE NAME AND ADDRESS Naval Medical Research & Development Command Bethesda, MD 20014		12. REPORT DATE July 1979
		13. NUMBER OF PAGES 16
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office) Bureau of Medicine & Surgery Department of the Navy Washington, D.C. 20372		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Bisinusoidal Analysis
Body Temperature
Blake-Colquhoun Data
Kanabrocki-Scheving Data
Monosinusoidal Analysis
Two-Wave Analysis

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

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